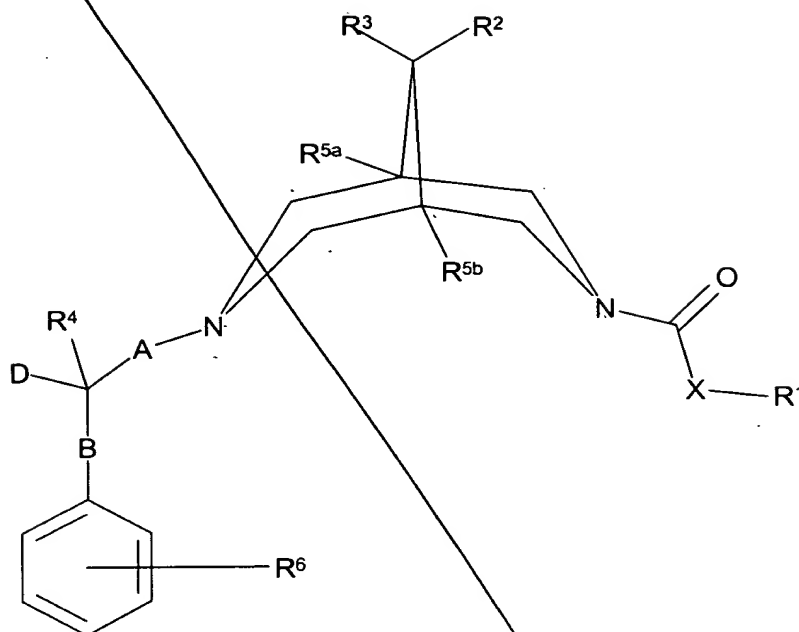


## Claims

1. A compound of formula I,



wherein

R<sup>1</sup> represents C<sub>1-12</sub> alkyl, -(CH<sub>2</sub>)<sub>a</sub>-aryl, or -(CH<sub>2</sub>)<sub>a</sub>-Het<sup>1</sup> (all of which are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, halo, cyano, nitro, C<sub>1-4</sub> alkyl and/or C<sub>1-4</sub> alkoxy);

a represents 0, 1, 2, 3, or 4;

Het<sup>1</sup> represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

$R^{5a}$  and  $R^{5b}$  independently represent H or  $C_{1-3}$  alkyl;

B<sup>2</sup>  
cont  
5  $R^2$  and  $R^3$  independently represent H,  $C_{1-4}$  alkyl (optionally substituted and/or terminated with one or more nitro or cyano groups),  $OR^7$ ,  $N(R^{7a})R^{7b}$ ,  $OC(O)R^8$  or together form  $-O-(CH_2)_2-O-$ ,  $-(CH_2)_3-$ ,  $-(CH_2)_4-$  or  $-(CH_2)_5-$ ;

$R^7$  and  $R^8$  independently represent H,  $C_{1-6}$  alkyl or  $-(CH_2)_b$ -aryl (which latter two groups are optionally substituted and/or terminated by one or more substituents selected from -OH, halo, cyano, nitro,  $C_{1-4}$  alkyl and/or  $C_{1-4}$  alkoxy);

$R^{7a}$  and  $R^{7b}$  independently represent H or  $C_{1-6}$  alkyl;

b represents 0, 1, 2, 3 or 4;

$R^4$  represents H or  $C_{1-6}$  alkyl;

15 D represents H,  $C_{1-4}$  alkyl, -OH, or  $-(CH_2)_cN(R^{10})(R^{11})$ ;

c represents 0, 1, 2, 3 or 4;

$R^{10}$  represents H,  $C_{1-6}$  alkyl,  $-(CH_2)_d$ -aryl,  $-C(NH)NH_2$ ,  $-S(O)_2R^{13}$ ,  $-[C(O)]_eN(R^{14})(R^{15})$ ,  $-C(O)R^{16}$  or  $-C(O)OR^{17}$ ;

20 e represents 1 or 2;

$R^{11}$  represents H,  $C_{1-6}$  alkyl,  $-C(O)R^{18}$  or  $-(CH_2)_f$ -aryl (which latter group is optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro,  $C_{1-6}$  alkyl and/or  $C_{1-6}$  alkoxy);

25  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$ ,  $R^{17}$  and  $R^{18}$  independently represent H,  $C_{1-6}$  alkyl, Het<sup>2</sup> or  $-(CH_2)_g$ -aryl (which latter three groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro,  $C_{1-6}$  alkyl and/or  $C_{1-6}$  alkoxy);

$R^{13}$  represents  $C_{1-6}$  alkyl, aryl or  $-(CH_2)_h$ -aryl (all of which are all optionally substituted and/or terminated (as appropriate) by one or more substituents chosen from halo, nitro,  $C_{1-6}$  alkyl and/or  $C_{1-6}$  alkoxy);

d, f, g and h independently represent 0, 1, 2, 3 or 4;

5 Het<sup>2</sup> represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

10  $R^6$  represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro,  $C_{1-6}$  alkyl (optionally terminated by  $-N(H)C(O)OR^{18a}$ ),  $C_{1-6}$  alkoxy,  $-C(O)N(H)R^{19}$ ,  $-NHC(O)N(H)R^{20}$ ,  $-N(H)S(O)_2R^{21}$  and/or  $-OS(O)_2R^{22}$ ;

$R^{19}$  and  $R^{20}$  independently represent H or  $C_{1-6}$  alkyl;

$R^{18a}$ ,  $R^{21}$  and  $R^{22}$  independently represent  $C_{1-6}$  alkyl;

15

A represents a single bond,  $C_{1-6}$  alkylene,  $-N(R^{23})(CH_2)_j-$ ,  $-O(CH_2)_j-$  or  $-(CH_2)_jC(H)(OR^{23})(CH_2)_k-$  (in which latter three groups, the  $-(CH_2)_j-$  group is attached to the bispidine nitrogen atom, and which latter four groups are all optionally substituted by one or more OH groups);

20 B represents a single bond,  $C_{1-4}$  alkylene,  $-(CH_2)_mN(R^{24})-$ ,  $-(CH_2)_mS(O)_n-$ ,  $-(CH_2)_mO-$  (in which three latter groups, the  $-(CH_2)_m-$  group is attached to the carbon atom bearing D and  $R^4$ ),  $-C(O)N(R^{24})-$  (in which latter group, the  $-C(O)-$  group is attached to the carbon atom bearing D and  $R^4$ ),  $-N(R^{24})C(O)O(CH_2)_m-$  or  $-N(R^{24})(CH_2)_m-$  (in which latter two groups, the

25  $N(R^{24})$  group is attached to the carbon atom bearing D and  $R^4$ );

j, k and m independently represent 0, 1, 2, 3 or 4;

n represents 0, 1 or 2;

$R^{23}$  represents H,  $C_{1-6}$  alkyl or  $C(O)R^{25}$ ;

$R^{24}$  represents H or  $C_{1-6}$  alkyl;

*B2  
cont*  
 $R^{25}$  represents H,  $C_{1-6}$  alkyl,  $Het^3$  or  $-(CH_2)_p$ -aryl (which latter two groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro,  $C_{1-6}$  alkyl and/or  $C_{1-6}$  alkoxy);

5  $Het^3$  represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

$p$  represents 0, 1, 2, 3 or 4;

10 or a pharmaceutically acceptable derivative thereof.

provided that:

(a) when D represents either H or -OH, and  $R^{5a}$  and  $R^{5b}$  both represent H, then at least one of  $R^2$  and  $R^3$  represents  $OR^7$ ,  $OC(O)R^8$  or  $C_{1-4}$  alkyl, which alkyl group is substituted and/or terminated with one or more nitro  
 15 or cyano groups; and

(b) when D represents -OH or  $-(CH_2)_cN(R^{10})R^{11}$  in which  $c$  represents 0, then:-

(i) A does not represent  $-N(R^{23})(CH_2)_j-$ ,  $-O(CH_2)_j-$  or  
 20  $-(CH_2)_jC(H)(OR^{23})(CH_2)_k-$  (in which  $k$  is 0); and/or

(ii)  $m$  does not represent 0 when B represents  $-(CH_2)_mN(R^{24})-$ ,  
 $-(CH_2)_mS(O)_n-$  or  $-(CH_2)_mO-$ .

2. A compound as claimed in Claim 1, wherein  $R^1$  represents optionally  
 25 substituted  $-(CH_2)_a$ -phenyl, in which  $a$  is 0, 1, 2 or 3, or optionally substituted, optionally unsaturated, linear, branched or cyclic,  $C_{1-18}$  alkyl (which latter group may also be interrupted by an oxygen atom).

*Sub  
F1.*

3. A compound as claimed in any Claim 1 or ~~Claim 2~~, wherein  $R^2$  represents H,  $OR^7$ ,  $-CH_2NO_2$  or  $-OC(O)R^8$  or together with  $R^3$  represents  $-O-(CH_2)_2-O-$ .

5 4. A compound as claimed in <sup>claim 1</sup> ~~any one of the preceding claims~~, wherein  $R^3$  represents H,  $OR^7$ ,  $C_{1-4}$  alkyl or together with  $R^2$  represents  $-O-(CH_2)_2-O-$ .

5 5. A compound as claimed in <sup>claim 1</sup> ~~any one of the preceding claims~~, wherein  $R^4$  represents H or  $C_{1-2}$  alkyl.

10 6. A compound as claimed in <sup>claim 1</sup> ~~any one of the preceding claims~~, wherein  $R^{5a}$  and  $R^{5b}$  either both represent H or both represent methyl.

15 7. A compound as claimed in <sup>claim 1</sup> ~~any one of the preceding claims~~, wherein  $R^6$  represents one or more substituents selected from  $C_{1-6}$  alkyl, cyano, nitro, amino or  $C(O)N(H)R^{19}$  or  $N(H)S(O)_2R^{21}$ .

8. A compound as claimed in <sup>claim 1</sup> ~~any one of the preceding claims~~, wherein X represents O.

20 9. A compound as claimed in <sup>claim 1</sup> ~~any one of the preceding claims~~, wherein A represents a single bond or linear, or branched,  $C_{1-4}$  alkylene (which group is also optionally interrupted by O).

25 10. A compound as claimed in <sup>claim 1</sup> ~~any one of the preceding claims~~, wherein B represents a single bond,  $C_{1-4}$  alkylene,  $-(CH_2)_mO-$  or  $-(CH_2)_mN(R^{24})-$  (in which latter two cases m is 1, 2 or 3).

9 11. A compound as claimed in <sup>claim 9</sup> ~~any one of the preceding claims~~, wherein when D represents  $-(CH_2)_cN(R^{10})(R^{11})$ , c represents 0, 1 or 2.

5 a 12. A compound as claimed in <sup>claim 1</sup> ~~any one of the preceding claims~~, wherein when D represents  $-(CH_2)_cN(R^{10})(R^{11})$ ,  $R^{10}$  represents H,  $C_{1-4}$  alkyl,  $-C(O)R^{16}$  (in which  $R^{16}$  is H,  $C_{1-3}$  alkyl or  $Het^2$ ),  $-C(O)OR^{17}$  (in which  $R^{17}$  is  $C_{1-5}$  alkyl, phenyl or  $C_{1-3}$  alkylphenyl),  $-C(NH)NH_2$  or  $-[C(O)]_c-N(H)R^{15}$  (in which  $R^{15}$  is H or  $C_{1-3}$  alkyl).

10 a 13. A compound as claimed in <sup>claim 9</sup> ~~any one of the preceding claims~~, wherein when D represents  $-(CH_2)_cN(R^{10})(R^{11})$ ,  $R^{11}$  represents H.

15 a 14. A pharmaceutical formulation including a compound as defined in <sup>claim 1</sup> ~~any one of Claims 1 to 13~~ in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.

20 a 15. A pharmaceutical formulation for use in the prophylaxis or the treatment of an arrhythmia, comprising a compound as defined in <sup>claim 1</sup> ~~any one of Claims 1 to 13~~.

a 16. A compound as defined in <sup>claim 7</sup> ~~any one of Claims 1 to 13~~ for use as a pharmaceutical.

25 a 17. A compound as defined in <sup>claim 1</sup> ~~any one of Claims 1 to 13~~ for use in the prophylaxis or the treatment of an arrhythmia.

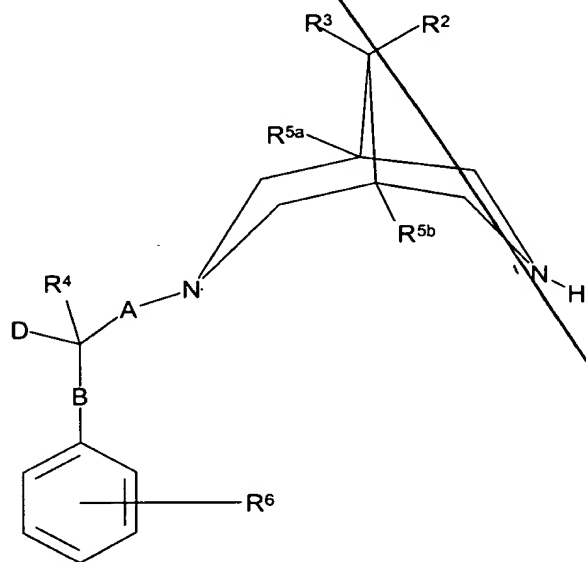
a 18. The use of a compound as defined in <sup>claim 1</sup> ~~any one of Claims 1 to 13~~ as active ingredient in the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.

19. The use as claimed in Claim 18, wherein the arrhythmia is an atrial or a ventricular arrhythmia.

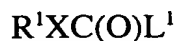
5 20. A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in <sup>claim 1</sup> ~~any one of Claims 1 to 13~~ to a person suffering from, or susceptible to, such a condition.

10 21. A process for the preparation of a compound of formula I as defined in Claim 1 which comprises:

(a) reaction of a compound of formula II,



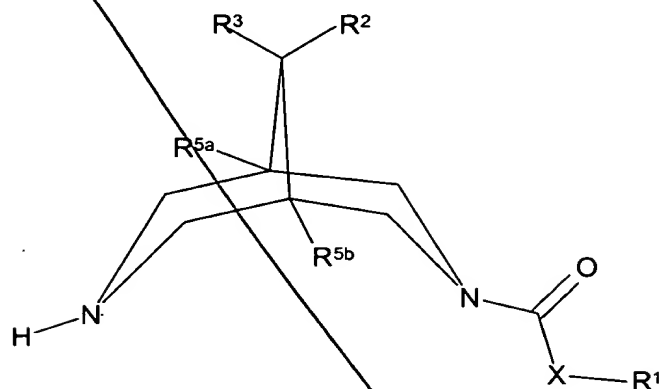
15 wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5a</sup>, R<sup>5b</sup>, R<sup>6</sup>, A, B and D are as defined in Claim 1 with a compound of formula III,



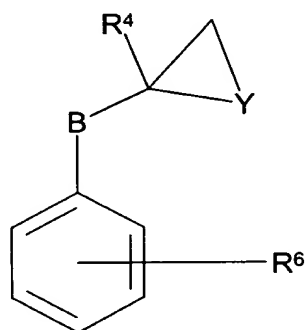
III

wherein L<sup>1</sup> represents a leaving group and R<sup>1</sup> and X are as defined in Claim 1;

(b) for compounds of formula I in which A represents  $\text{CH}_2$  and D represents  $-\text{OH}$  or  $\text{N}(\text{R}^{10})\text{H}$ , reaction of a compound of formula IV,



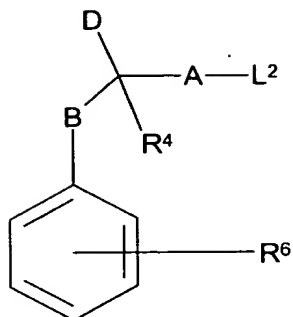
5 wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^{5a}$ ,  $\text{R}^{5b}$  and X are as defined in Claim 1, with a compound of formula V,



10 wherein Y represents O or  $\text{N}(\text{R}^{10})$  and  $\text{R}^4$ ,  $\text{R}^6$ ,  $\text{R}^{10}$  and B are as defined in Claim 1;

(c) reaction of a compound of formula IV, as defined above, with a compound of formula VI,

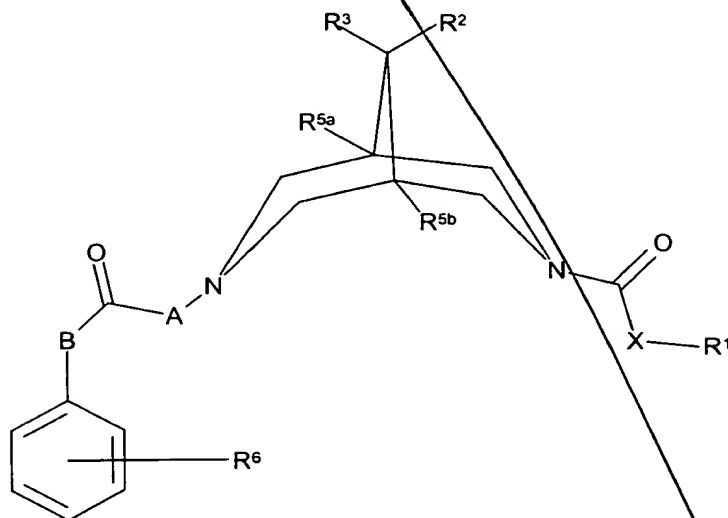




VI

wherein  $L^2$  represents a leaving group and  $R^4$ ,  $R^6$ , A, B and D are as defined in Claim 1;

- 5 (d) for compounds of formula I in which D represents H or OH and  $R^4$  represents H, reduction of a compound of formula VII,

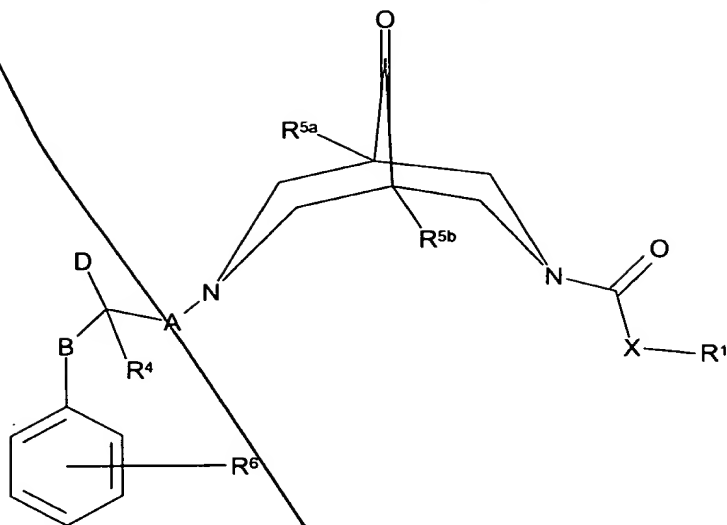


VII

- 10 wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^6$ , A, B and X are as defined in Claim 1;  
 (e) for compounds of formula I in which one of  $R^2$  and  $R^3$  represents H or OH and the other represents H, reduction of a corresponding compound of formula VIII,

76

VIII



wherein  $R^1$ ,  $R^4$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^6$ , A, B, D and X are as defined in Claim 1;

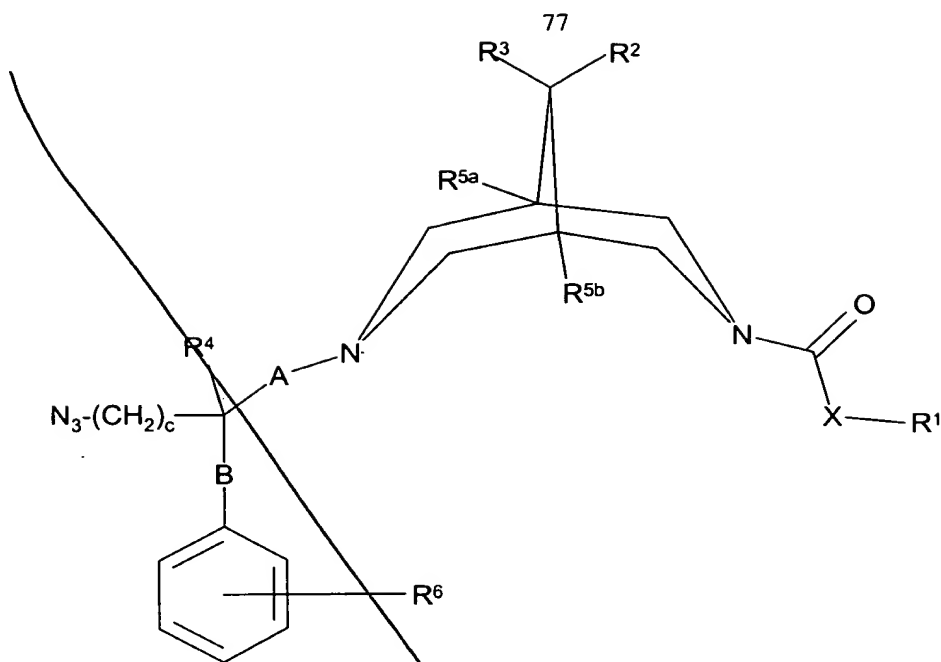
- (f) for compounds of formula I in which  $R^2$  and/or  $R^3$  represents  $OC(O)R^8$  and  $R^8$  is as defined in Claim 1, coupling of a corresponding compound of formula I in which  $R^2$  and/or  $R^3$  (as appropriate) represents OH and a compound of formula VIIIA,



VIIIA

wherein  $R^8$  is as defined in Claim 1;

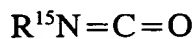
- (g) for compounds of formula I in which D represents  $-(CH_2)_cNH_2$ , reduction of a corresponding compound of formula IX,



wherein c, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5a</sup>, R<sup>5b</sup>, R<sup>6</sup>, A, B and X are as defined in Claim 1;

- (h) for compounds of formula I in which D represents -N(R<sup>11</sup>)C(O)NH(R<sup>15</sup>),  
 5 in which R<sup>11</sup> and R<sup>15</sup> are as defined in Claim 1 except that R<sup>11</sup> does not represent C(O)R<sup>18</sup>, reaction of a corresponding compound of formula I in which D represents -N(R<sup>11</sup>)H, in which R<sup>11</sup> is as defined in Claim 1 except that it does not represent C(O)R<sup>18</sup> in which R<sup>18</sup> is as defined in Claim 1, with a compound of formula X,

10



X

wherein R<sup>15</sup> is as defined in Claim 1;

- (i) for compounds of formula I in which D represents -N(H)[C(O)]<sub>2</sub>NH<sub>2</sub>, reaction of a corresponding compound of formula I in which D represents -NH<sub>2</sub> with oxalic acid diamide;
- 15 (j) for compounds of formula I in which D represents -N(R<sup>11</sup>)C(O)R<sup>16</sup>, in which R<sup>11</sup> and R<sup>16</sup> are as defined in Claim 1 except that R<sup>11</sup> does not represent C(O)R<sup>18</sup>, reaction of a corresponding compound of formula I in which D represents -N(R<sup>11</sup>)H, in which R<sup>11</sup> is as defined in Claim 1 except

that is does not represent  $C(O)R^{18}$  in which  $R^{18}$  is as defined in Claim 1, with a compound of formula XI,



wherein  $R^x$  represents a suitable leaving group and  $R^{16}$  is as defined in Claim 1;

(k) for compounds of formula I in which D represents  $-N(H)R^{10}$  and  $R^{10}$  is as defined in Claim 1 except that it does not represent H or  $-C(NH)NH_2$ , reaction of a corresponding compound of formula I wherein D represents  $-NH_2$  with a compound of formula XIA,



wherein  $R^{10a}$  represents  $R^{10}$  as defined in Claim 1 except that it does not represent H or  $-C(NH)NH_2$  and  $L^1$  is as defined above;

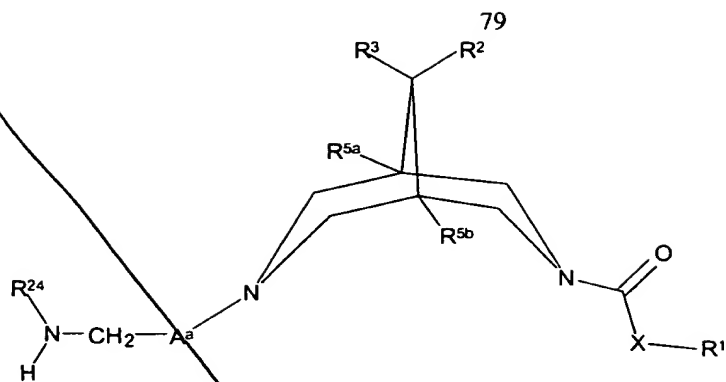
(l) for compounds of formula I which are bispidine-nitrogen N-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I;

(m) for compounds of formula I which are  $C_{1-4}$  alkyl quaternary ammonium salt derivatives, in which the alkyl group is attached to a bispidine nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XII,

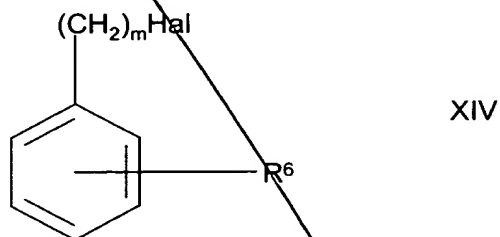


wherein  $R^a$  represents  $C_{1-4}$  alkyl and Hal represents Cl, Br or I;

(n) for compounds of formula I in which D and  $R^4$  both represent H, A represents  $C_{1-6}$  alkylene, B represents  $-N(R^{24})(CH_2)_m-$  and m and  $R^{24}$  are as defined in Claim 1, reaction of a compound of formula XIII,

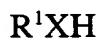


wherein A<sup>a</sup> represents C<sub>1-6</sub> alkylene and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>5a</sup>, R<sup>5b</sup>, R<sup>24</sup> and X are as defined in Claim 1 with a compound of formula XIV,



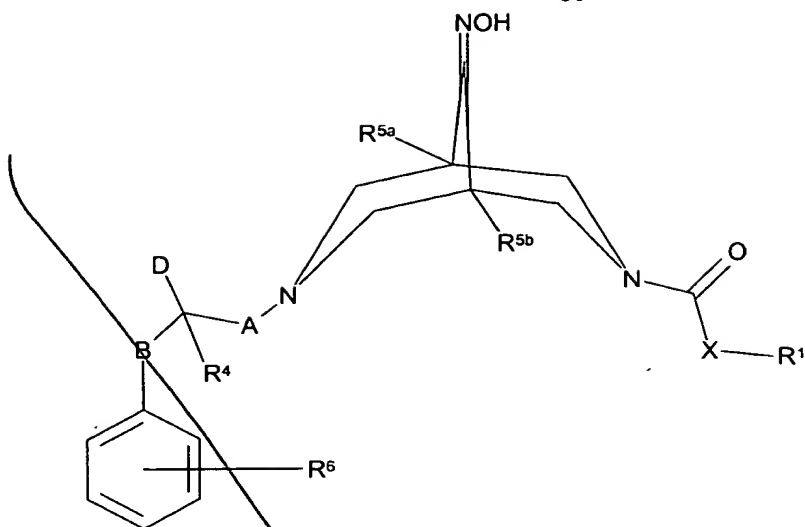
wherein R<sup>6</sup>, m are as defined in Claim 1 and Hal is as defined above;

(o) reaction of a compound of formula II, as defined above, with a compound of formula XV,



wherein R<sup>1</sup> and X are as defined in Claim 1, in the presence of 1,1'-carbonyldiimidazole;

(p) for compounds of formula I in which one of R<sup>2</sup> and R<sup>3</sup> represents -NH<sub>2</sub> and the other represents H, reduction of a compound of formula XVA,



wherein  $R^1$ ,  $R^4$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^6$ , A, B, D and X are as defined in Claim 1;

- (q) for compounds of formula I in which one or both of  $R^2$  and  $R^3$  represent  $-N(R^{7a})R^{7b}$  in which one or both of  $R^{7a}$  and  $R^{7b}$  represents  $C_{1-6}$  alkyl, alkylation of a corresponding compound of formula I in which  $R^2$  and/or  $R^3$  represent  $-N(R^{7a})R^{7b}$  (as appropriate) in which  $R^{7a}$  and/or  $R^{7b}$  (as appropriate) represent H, using a compound of formula XXIB,



XXIB

- wherein  $R^{7c}$  represents  $C_{1-6}$  alkyl and  $L^1$  is as defined above;

(r) conversion of one  $R^6$  substituent to another; or

(s) deprotection of a protected derivative of a compound of formula I as defined in Claim 1.

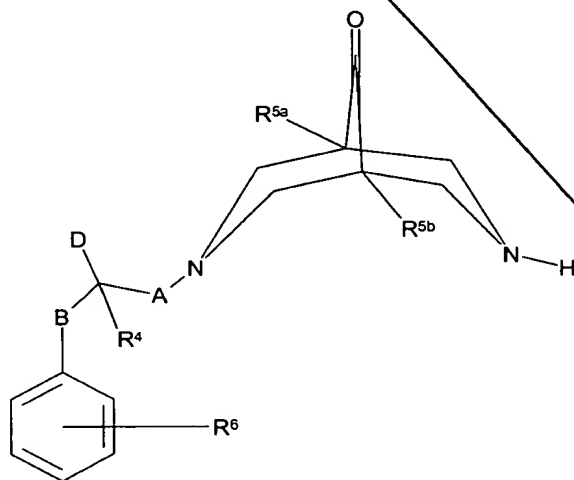
22. A compound of formula II as defined in Claim 21, or a protected derivative thereof, provided that when  $R^{5a}$  and  $R^{5b}$  both represent H, then D does not represent H or OH.

23. A compound of formula IV as defined in Claim 21, or a protected derivative thereof, provided that when  $R^{5a}$  and  $R^{5b}$  both represent H, then at least one of  $R^2$  and  $R^3$  represents  $OR^7$ ,  $OC(O)R^8$  or  $C_{1-4}$  alkyl, which alkyl

group is substituted and/or terminated with one or more nitro or cyano groups.

24. A compound of formula VIII as defined in Claim 21, or a protected derivative thereof, provided that when  $R^{5a}$  and  $R^{5b}$  both represent H, then D does not represent H or OH.

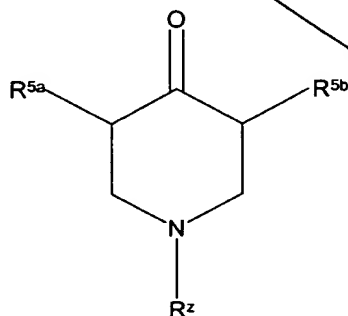
25. A compound of formula XVII,



XVII

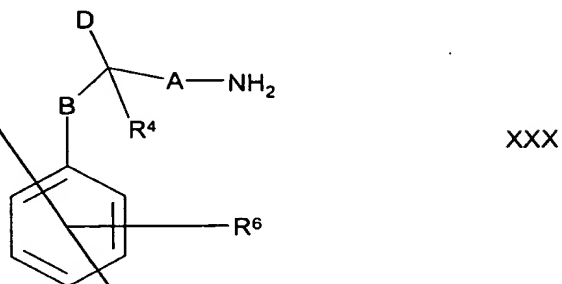
- wherein  $R^4$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^6$ , A, B and D are as defined in Claim 1, or a protected derivative thereof, provided that when  $R^{5a}$  and  $R^{5b}$  both represent H, then D does not represent H or OH.

26. A process for the preparation of a compound of formula VIII, XVII, XVIII or XXVIII, as defined herein, which comprises reaction of a compound of formula XXIX,



XXIX

(1) a compound of formula XXX,



or a protected derivative thereof, wherein  $R^4$ ,  $R^6$ , A, B and D are as defined in Claim 1; or

(2)  $\text{NH}_3$  (or a protected derivative thereof),

in all cases in the presence of a formaldehyde.